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 NEWS 1          Web Page for STN Seminar Schedule - N. America
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 NEWS 3  OCT 07  EPFULL enhanced with full implementation of EPC2000
 NEWS 4  OCT 07  Multiple databases enhanced for more flexible patent
                 number searching
 NEWS 5  OCT 22  Current-awareness alert (SDI) setup and editing
                 enhanced
 NEWS 6  OCT 22  WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT
                 Applications
 NEWS 7  OCT 24  CHEMLIST enhanced with intermediate list of
pre-registered REACH substances
 NEWS 8  NOV 21  CAS patent coverage to include exemplified prophetic
                 substances identified in English-, French-,
                 German-, and Japanese-language basic patents from
2004-present
 NEWS 9  NOV 26  MARPAT enhanced with FSORT command
 NEWS 10 NOV 26  MEDLINE year-end processing temporarily halts
                 availability of new fully-indexed citations
 NEWS 11 NOV 26  CHEMSAFE now available on STN Easy
 NEWS 12 NOV 26  Two new SET commands increase convenience of STN
                 searching
 NEWS 13 DEC 01  ChemPort single article sales feature unavailable
 NEWS 14 DEC 12  GBFULL now offers single source for full-text
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3099 MTOR/BI          2720 MTOR/AB          267065
MAMMALIAN/BI          135423 MAMMALIAN/AB
414926 TARGET/BI          381126 TARGET/AB
8160 RAPAMYCIN/BI          6338 RAPAMYCIN/AB
2525 MAMMALIAN(W)TARGET(2A)RAPAMYCIN
L1       3645 (MTOR OR
(MAMMALIAN(W)TARGET(2A)RAPAMYCIN))/BI,AB

=> s (p53 or tp53 or p21)/bi,ab     46247 P53/BI
40683 P53/AB          14274 TP53/BI          2187
TP53/AB          67509 P21/BI          65470 P21/AB
L2      110794 (P53 OR TP53 OR P21)/BI,AB

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=> s l1 and l2
L3       156 L1 AND L2

=> s l3 not 2008/py   1524818 2008/PY
L4       114 L3 NOT 2008/PY

=> s l4 not 2007/py   1688592 2007/PY
L5        71 L4 NOT 2007/PY

=> s l5 not 2006/py   1573757 2006/PY
L6        44 L5 NOT 2006/PY
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=> s l6 not 2005/py 1425346 2005/PY
L7 28 L6 NOT 2005/PY

=> d his
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FILE 'CAPLUS' ENTERED AT 10:13:54 ON 17 DEC 2008
L1 3645 S (MTOR OR (MAMMALIAN(W)TARGET(2A)RAPAMYCIN))/BI,AB
L2 110794 S (P53 OR TP53 OR P21)/BI,AB
L3 156 S L1 AND L2
L4 114 S L3 NOT 2008/PY
L5 71 S L4 NOT 2007/PY
L6 44 S L5 NOT 2006/PY
L7 28 S L6 NOT 2005/PY

=> d l7 1-28 bib ab

L7 ANSWER 1 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2008:1493745 CAPLUS <<LOGINID::20081217>>
TI Inhibition of ***mTOR*** enhances chemosensitivity in hepatocellular carcinoma
AU Tam, Ka Ho; Yang, Zhen Fan; Lau, Chi Keung; Lam, Chi Tat; Pang, Roberta W. C.; Poon, Ronnie T. P.
CS Center for Cancer Research, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Pokfulam, Hong Kong, 102, Peop. Rep. China
SO Cancer Letters (Shannon, Ireland) (2009), 273(2), 201-209 CODEN: CALEDQ; ISSN: 0304-3835
PB Elsevier Ireland Ltd.
DT Journal
LA English
AB The present study investigated the effect of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***) inhibition on HCC cells in vitro and in vivo, either alone or in combination with cytotoxic agents. In vitro, HCC cell lines were exposed to RAD001, an ***mTOR*** inhibitor, either alone or in combination with cisplatin. Alone, RAD001 suppressed cell proliferation in all cell lines tested, but did not induce apoptosis. RAD001 in combination with cisplatin induced a significant increase in the no. of apoptotic cells, downregulated the expression of pro-survival mols., Bcl-2, survivin and cyclinD1, and increased the cleavage of PARP, compared to RAD001 or cisplatin alone. Transfection of ***p53*** into the Hep3B cell line increased the sensitivity of tumor cells to cisplatin. The suppression of HCC tumor growth in vivo was enhanced by RAD001 combined with cisplatin, accompanied by a significant increase in the no. of apoptotic cells in tumor tissues. This study demonstrates that inhibition of ***mTOR*** suppresses tumor growth and sensitizes tumor cells to chemocytotoxic agents.

L7 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:886987 CAPLUS <<LOGINID::20081217>>
DN 142:190423
TI Bcl-2 and CCND1/CDK4 expression levels predict the cellular effects of ***mTOR*** inhibitors in human ovarian carcinoma
AU Aguirre, D.; Boya, P.; Bellet, D.; Faivre, S.; Troalen, F.; Benard, J.; Saulnier, P.; Hopkins-Donaldson, S.; Zangemeister-Wittke, U.; Kroemer, G.; Raymond, E.
CS Department of Clinical Biology, Department of Medicine, Institute Gustave-Roussy, Villejuif, 94805, Fr.
SO Apoptosis (2004), 9(6), 797-805 CODEN: APOPFN; ISSN: 1360-8185
PB Kluwer Academic Publishers
DT Journal
LA English
AB Mol. markers enabling the prediction of sensitivity/resistance to rapamycin may facilitate further clin. development of rapamycin and its derivs. as anticancer agents. In this study, several human ovarian cancer cell lines (IGROV1, OVCAR-3, A2780, SK-OV-3) were evaluated for susceptibility to rapamycin-mediated growth inhibition. The differential expression profiles of genes coding for proteins known to be involved in the ***mTOR*** signaling pathway, cell cycle control and apoptosis were studied before and after drug exposure by RT-PCR. In cells exposed to rapamycin, we obsd. a dose-dependent downregulation of CCND1 (cyclin D1) and CDK4 gene expression and late G1 cell cycle arrest. Among these cell lines, SK-OV-3 cells resistant to both rapamycin and RAD001 were the sole to show the expression of the anti-apoptotic gene Bcl-2. Bcl-2/bclxL-specific antisense oligonucleotides restored the sensitivity of SK-OV-3 cells to apoptosis induction by rapamycin and RAD001. These results indicate that baseline Bcl-2 expression and therapy-induced downexpression of CCND1 and CDK4 may be regarded as mol. markers enabling the prediction and follow-up of the cellular effects on cell cycle and apoptosis induction of rapamycin in ovarian cancer. Furthermore, strategies to down regulate Bcl-2 in ovarian cancer may prove useful in combination with rapamycin or RAD001 for ovarian cancer.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:847052 CAPLUS <<LOGINID::20081217>>
DN 142:3890
TI Akt-1 expression level regulates CNS precursors
AU Sinor, Amy D.; Lillien, Laura
CS Department of Neurobiology and Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA
SO Journal of Neuroscience (2004), 24(39), 8531-8541 CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
AB Although most cells in the embryonic mouse cortex express the serine-threonine kinase Akt-1, a small population of progenitors expresses Akt-1 protein at a higher level. To det. the functional significance of this difference, we used a retrovirus to increase Akt-1 expression in cortical progenitors. Increased Akt expression enhanced Akt activation after growth factor stimulation of progenitors. In vivo, it promoted retention in progenitor layers, the ventricular zone and subventricular zone. In vitro, it enhanced proliferation and survival, but did not impair migration. Moreover, it increased the proportion of stem cells, defined by a self-renewal assay. These effects did not depend on the Akt substrate ***p21*** (Cip1). In contrast, rapamycin, an inhibitor of ***mTOR*** (***mammalian*** ***target*** of ***rapamycin***), altered effects of elevated Akt-1 selectively: it eliminated the increase in stem cells and reduced the proliferative response, but had no effect on survival. The ability of elevated Akt-1 to increase the self-renewing population therefore depends on a rapamycin-sensitive mechanism (presumably inhibition of ***mTOR*** activity) but not on ***p21*** (Cip1), and can be distinguished from its effects on the proliferation and survival of other types of progenitors. Our findings suggest that expression of a high level of Akt-1 by a subpopulation of cortical progenitors biases their responses to extrinsic signals to increase their survival, proliferation, and/or self-renewal. Heterogeneity in Akt-1 level among progenitors could therefore allow cells that share a

microenvironment to respond differently to the same extrinsic signals.
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:777698 CAPLUS <<LOGINID::20081217>>
DN 142:235440
TI Expression, purification, crystallization and preliminary structural characterization of the GTPase domain of human Rheb
AU Yu, Yadong; Chang, Yonggang; Li, Sheng; Hu, Hongyu; Huang, Qiuhua; Ding, Jianping
CS Key Laboratory of Proteomics, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SO Acta Crystallographica, Section D: Biological Crystallography (2004), D60(10), 1883-1887 CODEN: ABCRE6; ISSN: 0907-4449
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Ras homolog enriched in brain (Rheb) represents a unique group of small GTPases and shares moderate sequence identity with the Ras/Rap subfamily. It acts downstream of nutrient signaling as the direct target of the tuberous sclerosis complex (TSC) and upstream of ***mTOR*** /S6K1/4EBP in the insulin-signaling pathway. The GTPase domain of human Rheb (hRheb) has been recombinantly expressed in Escherichia coli, purified and cocrystd. in complexes with GDP, GTP and GppNHp using the hanging-drop vapor-diffusion method. Crystals of the hRheb-GDP complex belong to space group P212121, with unit-cell parameters a = 44.5, b = 52.3, c = 70.6 .ANG.. The hRheb-GppNHp complex crystd. in two crystal forms: one has the same space group and unit-cell parameters as the hRheb-GDP complex and the other belongs to space group C2221, with unit-cell parameters a = 102.9, b = 99.2, c = 48.0 .ANG.. The hRheb-GTP complex also crystd. in two crystal forms: one belongs to space group C2221, with unit-cell parameters a = 102.4, b = 98.3, c = 47.9 .ANG., and the other belongs to space group ***P21*** , with unit-cell parameters a = 77.3, b = 47.9, c = 71.9 .ANG., .beta. = 89.0.degree.. All these crystals diffract X-rays to better than 2.8 .ANG. resoln. and at least one diffraction data set has been collected for each crystal form using an inhouse R-AXIS IV++ diffractometer. Structural studies of hRheb in complexes with various substrates may provide insights into the recognition and specificity of substrate and the catalytic mechanism of mammalian Rhebs and shed light on the biol. functions of Rhebs in the ***mTOR*** signaling pathway.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:694495 CAPLUS <<LOGINID::20081217>>
DN 141:204170
TI Inhibition of ***Mammalian*** ***Target*** of ***Rapamycin*** Activates Apoptosis Signal-regulating Kinase 1 Signaling by Suppressing Protein Phosphatase 5 Activity
AU Huang, Shile; Shu, Lili; Easton, John; Harwood, Franklin C.; Germain, Glen S.; Ichijo, Hidenori; Houghton, Peter J.
CS Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105-2794, USA
SO Journal of Biological Chemistry (2004), 279(35), 36490-36496 CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Under serum-free conditions, rapamycin, an inhibitor of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***), induces a cellular stress response characterized by rapid and sustained activation of the apoptosis signal-regulating kinase 1 (ASK1) signaling pathway and selective apoptosis of cells lacking functional ***p53*** . Here we have investigated how ***mTOR*** regulates ASK1 signaling using ***p53*** -mutant rhabdomyosarcoma cells. In Rh30 cells, ASK1 was found to phys. interact with protein phosphatase 5 (PP5), previously identified as a neg. regulator of ASK1. Rapamycin did not affect either protein level of PP5 or assocn. of PP5 with ASK1. Instead, rapamycin caused rapid dissocn. of the PP2A-B" regulatory subunit (PR72) from the PP5-ASK1 complex, which was assocd. with reduced phosphatase activity of PP5. This effect was dependent on expression of eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). Down-regulation of PP5 activity by rapamycin coordinately activated ASK1, leading to elevated phosphorylation of c-Jun. Amino acid deprivation, which like rapamycin inhibits ***mTOR*** signaling, also inhibited PP5 activity, caused rapid dissocn. of PR72, and activated ASK1 signaling. Overexpression of PP5, but not the PP2A catalytic subunit, blocked rapamycin-induced phosphorylation of c-Jun, and protected cells from rapamycin-induced apoptosis. The results suggest that PP5 is downstream of ***mTOR*** , and pos. regulated by the ***mTOR*** pathway. The findings suggest that in the absence of serum factors, ***mTOR*** signaling suppresses apoptosis through pos. regulation of PP5 activity and suppression of cellular stress.
RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:627302 CAPLUS <<LOGINID::20081217>>
DN 141:171919
TI Co-inhibition of epidermal growth factor receptor and type 1 insulin-like growth factor receptor synergistically sensitizes human malignant glioma cells to CD95L-induced apoptosis
AU Steinbach, Joachim P.; Eisenmann, Christine; Klumpp, Andrea; Weller, Michael
CS Laboratory of Molecular Neuro-Oncology, Department of Neurology, School of Medicine, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, 72076, Germany
SO Biochemical and Biophysical Research Communications (2004), 321(3), 524-530 CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
AB Inhibition of epidermal growth factor receptor (EGFR) signaling sensitizes human malignant glioma cells to death ligand-induced apoptosis. However, tumor cells may compensate the loss of EGFR signaling by activation of the type 1 insulin-like growth factor receptor (IGF-1R). We here report that antagonism of the IGF-1R with the small-mol. inhibitor AG1024 in combination with inhibitors of the EGFR synergistically sensitizes human malignant glioma cells to CD95L-induced apoptosis. This cell death is ***p53*** -independent, but requires caspase 8 activity. The levels of the receptor, CD95, are not altered by the inhibitors alone or in combination. Anal. of the downstream signaling pathways reveals synergistic inhibition of ribosomal protein S6 phosphorylation by inhibitor co-treatment, suggesting an involvement of the ***mammalian*** ***target*** of ***rapamycin*** pathway. These findings suggest that adding inhibitors of IGF-1R may be a strategy to overcome escape from the anti-apoptotic effects of EGFR inhibition in malignant gliomas.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:583221 CAPLUS <<LOGINID::20081217>>
DN 141:188804
TI An activated ***mTOR*** mutant supports growth factor-independent, nutrient-dependent cell survival
AU Edinger, Aimee L.; Thompson, Craig B.
CS Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, PA, 19104, USA
SO Oncogene (2004), 23(33), 5654-5663 CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
AB In yeast, TOR couples cellular growth and metab. to the availability of extracellular nutrients. In contrast, mammalian TOR kinase activity has been reported to be regulated by growth factor stimulation via the PI3K/Akt pathway. Consistent with this, growth factor deprivation results in dephosphorylation of the ***mTOR*** target proteins p70S6k and 4EBP1 in the face of abundant extracellular nutrients. To det. whether the activation of ***mTOR*** was sufficient to support cell survival in the absence of other growth factor-mediated signal transduction, we evaluated the ability of a growth factor-independent ***mTOR*** mutant, .DELTA.TOR, to protect cells from growth factor deprivation. .DELTA.TOR- but not wild-type ***mTOR*** -expressing cells were protected from many of the sequelae of growth factor deprivation including amino-acid transporter degrdn., redn. of the glycolytic rate, cellular atrophy, decreased mitochondrial membrane potential, and Bax activation. Furthermore, .DELTA.TOR expression increased growth factor-independent, nutrient-dependent cell survival and enhanced the ability of ***p53*** -/-MEFs to form colonies in soft agar. These results suggest that activating mutations of ***mTOR*** can contribute to apoptotic resistance and might contribute to cellular transformation.
RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:581125 CAPLUS <<LOGINID::20081217>>
DN 141:150609
TI AMP-activated protein kinase activators can inhibit the growth of prostate cancer cells by multiple mechanisms
AU Xiang, Xiaoqin; Saha, Asish K.; Wen, Rong; Ruderman, Neil B.; Luo, Zhijun
CS Diabetes Research Unit, Section of Endocrinology, Department of Medicine, Boston University School of Medicine, Boston, MA, 02118, USA
SO Biochemical and Biophysical Research Communications (2004), 321(1), 161-167 CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier Science
DT Journal
LA English
AB Prostate cancer cells require high rates of de novo fatty acid synthesis and protein synthesis for their rapid growth. The authors report here that the growth of these cells is markedly diminished by incubation with activators of AMP-activated protein kinase (AMPK), a fuel-sensing enzyme that has been shown to diminish both of these processes in intact tissues. Inhibition of cell growth was obsd. when AMPK was activated by either 5-aminoimidazole-4-carboxamide riboside (AICAR) or the thiazolidinedione rosiglitazone. Thus, a 90% inhibition of the growth of androgen-independent (DU145, PC3) and androgen-sensitive (LNCaP) cells was achieved after 4 days of exposure to one or both of these agents. Where studied, this was assocd. with a decrease in the concn. of malonyl Co-A, an intermediate of de novo fatty acid synthesis, and an increase in expression of the cell cycle inhibitor ***p21*** . In addn., AICAR inhibited two key enzymes involved in protein synthesis, ***mTOR*** and p70S6K, and blocked the ability of the androgen R1881 to increase cell growth and the expression of two enzymes for de novo fatty acid synthesis, acetyl Co-A carboxylase and fatty acid synthase, in the LNCaP cells. The results suggest that AMPK is a potential target for the treatment of prostate cancer.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:562935 CAPLUS <<LOGINID::20081217>>
DN 141:86293
TI Phospholipase D elevates the level of MDM2 and suppresses DNA damage-induced increases in ***p53***
AU Hui, Li; Abbas, Tarek; Pielak, Rafal M.; Joseph, Troy; Bargonetti, Jill; Foster, David A.
CS Department of Biological Sciences, Hunter College of the City University of New York, New York, NY, 10021, USA
SO Molecular and Cellular Biology (2004), 24(13), 5677-5686 CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB Phospholipase D (PLD) has been reported to generate survival signals that prevent apoptosis induced by serum withdrawal. We have now found that elevated expression of PLD also suppresses DNA damage-induced apoptosis. Since DNA damage-induced apoptosis is often mediated by ***p53*** , we examd. the effect of elevated PLD expression on the regulation of ***p53*** stabilization. We report here that PLD suppresses DNA damage-induced increases in ***p53*** stabilization in cells where PLD has been shown to provide a survival signal. Elevated expression of PLD also led to increased expression of the ***p53*** E3 ubiquitin ligase MDM2 and increased turnover of ***p53*** . PLD1-stimulated increases in MDM2 expression and suppression of ***p53*** activation were blocked by inhibition of ***mTOR*** and the mitogen-activated protein kinase pathway. Although PLD did not activate the phosphatidylinositol 3-kinase (PI3K)/Akt survival pathway the basal levels of PI3K activity were partially required for PLD1-induced increases in MDM2. These data provide evidence that survival signals generated by PLD involve suppression of the ***p53*** response pathway.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:317541 CAPLUS <<LOGINID::20081217>>
DN 140:389311
TI The role of translation in neoplastic transformation from a pathologist's point of view
AU Rosenwald, Igor B.
CS Division of Hematopathology, Department of Pathology, University of New Mexico, Albuquerque, NM, 87131, USA
SO Oncogene (2004), 23(18), 3230-3247 CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group

DT Journal; General Review
LA English
AB A review. Increased cell proliferation, which is a hallmark of aggressive malignant neoplasms, requires a general increase in protein synthesis and a specific increase in the synthesis of replication-promoting proteins. Transient increase in the general protein synthesis rate, as well as preferential translation of specific mRNAs coding for growth promoting proteins (e.g. cyclin D1), takes place during normal mitogenic response. A no. of extensively studied growth signal transduction pathways (Ras, PI3K, MAPK, ***mTOR*** -dependent pathways) activate the function and expression of various components of the translational machinery. In abnormal situations, constitutive activation of signal transduction pathways (e.g. oncogenic activation of Ras or Myc) leads to continuous upregulation of key elements of translational machinery. On the other hand, tumor suppressor genes (***p53*** , pRb) downregulate ribosomal and tRNA synthesis, and their inactivation results in uncontrolled prodn. of these translational components. During recent years, a significant effort has been dedicated to detg. whether expression of translation factors is increased in human tumors using clin. biopsy specimens. The results of these studies indicate that expression of particular translation initiation factors is not always increased in human neoplasms. The pattern of expression is characteristic for a particular tumor type. For example, eIF-4E is usually increased in bronchioloalveolar carcinomas but not in squamous cell carcinomas of the lung. Interestingly, in certain highly proliferative and aggressive neoplasms (e.g. squamous cell carcinoma of the lung, melanoma), the expression of eIF-4E is barely detectable. These findings suggest that mechanisms for increasing general protein synthesis in various neoplasms differ significantly. Finally, the possibility of qual. alterations in the translational machinery, rather than a simple increase in the activity of its components, is discussed along with the possibility of targeting those qual. differences for tumor therapy.
RE.CNT 177 THERE ARE 177 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:248803 CAPLUS <<LOGINID::20081217>>
DN 140:318513
TI Induction of ***p21*** and p27 expression by amino acid deprivation of HepG2 human hepatoma cells involves mRNA stabilization
AU Leung-Pineda, Van; Pan, YuanXiang; Chen, Hong; Kilberg, Michael S.
CS Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville, FL, 32610-0245, USA
SO Biochemical Journal (2004), 379(1), 79-88 CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press Ltd.
DT Journal
LA English
AB MRNA abundance for a no. of genes is increased by amino acid limitation. From an array screening study in HepG2 human hepatoma cells, it was established that one set of genes affected by amino acid availability is the set assocd. with cell-cycle control. The present study describes the increased expression of both mRNA and protein for the cyclin-dependent kinase inhibitors ***p21*** and p27 in response to deprivation of HepG2 cells for a single essential amino acid, histidine. The increase in ***p21*** and p27 mRNA content depended on de novo protein synthesis and involved a post-transcriptional mRNA stabilization component. For ***p21*** , increase in mRNA by histidine depletion appeared to be independent of ***p53*** transactivation, and the abs. level of ***p53*** protein was unaffected by this treatment. Histidine limitation caused an increase in the phosphorylation of ERK1/ERK2 (extracellular-signal-regulated kinase), and inhibition of the ERK signal transduction pathway resulted in a redn. in the starvation-dependent increase in ***p21*** mRNA. Blockade of the phosphoinositide 3-kinase and ***mTOR*** (***mammalian*** ***target*** of ***rapamycin***) pathways also blunted the increase in ***p21*** mRNA content. These results document the amino acid-dependent control of the synthesis of specific cell-cycle regulators and help to explain the block at G1 phase after amino acid limitation.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:51863 CAPLUS <<LOGINID::20081217>>
DN 140:108872
TI N6-Methyldeoxyadenosine, a nucleoside commonly found in prokaryotes, induces C2C12 myogenic differentiation
AU Charles, Marie-Pierre; Ravanat, Jean-Luc; Adamski, Daniele; D'Orazi, Gabriella; Cadet, Jean; Favier, Alain; Berger, Francois; Wion, Didier
CS INSERM U318, CHU Michallon, Grenoble, 38043, Fr.
SO Biochemical and Biophysical Research Communications (2004), 314(2), 476-482 CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier Science
DT Journal
LA English
AB N6-methyl-2'-deoxyadenosine (MedAdo) is a nucleoside naturally found in prokaryotic DNA. Interestingly, the N6-methylation of adenine in DNA seems to have been counter-selected during the course of evolution since MedAdo has not been detected in mammalian DNA until now. We show here that treatment with MedAdo induces myogenesis in C2C12 myoblasts. The presence of MedAdo in C2C12 DNA was investigated using a method based on HPLC coupled to electrospray ionization tandem mass spectrometry which is several thousand fold more sensitive than assays used previously. By this procedure, MedAdo is detected in the DNA from MedAdo-treated cells but remains undetectable in the DNA from control cells. Furthermore, MedAdo regulates the expression of ***p21*** , myogenin, ***mTOR*** , and MHC. Interestingly, in the pluripotent C2C12 cell line, MedAdo drives the differentiation towards myogenesis only. Thus, the biol. effect of MedAdo is suppressed in the presence of BMP-2 which transdifferentiates C2C12 from myogenic into osteogenic lineage cells. Taken together these results point to MedAdo as a novel inducer of myogenesis and further extends the differentiation potentialities of this methylated nucleoside. Furthermore, these data raise the intriguing possibility that the biol. effects of MedAdo on cell differentiation may have led to its counter-selection in eukaryotes.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:992960 CAPLUS <<LOGINID::20081217>>
DN 140:176035
TI Frap, FKBP12 rapamycin-associated protein, is a candidate gene for the plasmacytoma resistance locus Pctr2 and can act as a tumor suppressor gene

AU Bliskovsky, Valery; Ramsay, Edward S.; Scott, John; DuBois, Wendy; Shi, Wei; Zhang, Shuling; Qian, Xiaolan; Lowy, Douglas R.; Mock, Beverly A.
CS Laboratories of Genetics, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892-4258, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(25), 14982-14987 CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Susceptibility to mouse plasmacytomagenesis is a complex genetic trait controlled by several Pctr loci (Pctr1, Pctr2, etc). Congenic strain anal. narrowed the genetic interval surrounding the Pctr2 locus, and genes identified in the interval were sequenced from susceptible BALB/c and resistant DBA/2 mice. Frap (FKBP12 rapamycin-assocd. protein, ***mTOR*** , RAFT) was the only gene differing in amino acid sequence between alleles that correlated with strain sensitivity to tumor development. The in vitro kinase activity of the BALB/c FRAP allele was lower than the DBA/2 allele; phosphorylation of ***p53*** and PHAS1/4EBP1 (properties of heat and acid stability/eukaryotic initiation factor 4E-binding protein) and autophosphorylation of FRAP were less efficient with the BALB/c allele. FRAP also suppressed transformation of NIH 3T3 cells by ras, with DBA/2 FRAP being more efficient than BALB/c FRAP. Rapamycin, a specific inhibitor of FRAP, did not inhibit growth of plasmacytoma cell lines. These studies identify Frap as a candidate tumor suppressor gene, in contrast to many reports that have focused on its prooncogenic properties. Frap may be similar to Tgfb and E2f in exerting both pos. and neg. growth-regulatory signals, depending on the timing, pathway, or tumor system involved. The failure of rapamycin to inhibit plasma cell tumor growth suggests that FRAP antagonists may not be appropriate for the treatment of plasma cell tumors. Pctr2 joins Pctr1 in possessing alleles that modify susceptibility to plasmacytomagenesis by encoding differences in efficiency of function (efficiency alleles), rather than all-or-none, gain-of-function, or loss-of-function alleles. By analogy, human cancer may also result from the combined effects of several inefficient alleles.
RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:920789 CAPLUS <<LOGINID::20081217>>
DN 140:402106
TI Kinase activities associated with ***mTOR***
AU Yonezawa, K.; Yoshino, K.-I.; Tokunaga, C.; Hara, K.
CS Biosignal Research Center, Kobe University, Kobe, 657-8501, Japan
SO Current Topics in Microbiology and Immunology (2004), 279(TOR: Target of Rapamycin), 271-282 CODEN: CTMIA3; ISSN: 0070-217X
PB Springer-Verlag
DT Journal; General Review
LA English
AB A review. Although ***mTOR*** is a member of the PI-kinase-related kinase family, ***mTOR*** possesses serine-threonine protein kinase activities, which phosphorylates itself and exogenous substrates. The ***mTOR*** autophosphorylates in vitro and is phosphorylated in vivo on serine residues. Ser2481, which is located in a His-Ser-Phe motif near the conserved carboxyl-terminal ***mTOR*** tail, has been reported as an autophosphorylation site in vivo and in vitro. The significance of the autophosphorylation remains unclear. Another phosphorylation site on ***mTOR*** in vivo is Ser2448. This site appears not to be an autophosphorylation site but a site potentially phosphorylated by protein kinase B (PKB). The ***mTOR*** immunopurified from cultured cells or tissues phosphorylates in vitro p70 S6 kinase (p70) .alpha. and p70.beta., mainly on Thr412 or Thr401, resp., located in a Phe-Thr-Tyr motif. Another exogenous substrate phosphorylated by immunopurified ***mTOR*** in vitro is elF4E-binding protein 1 (4E-BP1) at sites corresponding to those phosphorylated in vivo during insulin stimulation in a Ser/Thr-Pro motif. Recently, raptor, a 150-kDa TOR-binding protein that contains a carboxyl-terminal WD-repeat domain, was discovered as a scaffold for the ***mTOR*** -catalyzed phosphorylation of 4E-BP1 and for the ***mTOR*** -mediated phosphorylation and activation of p70.alpha.. Other potential substrates phosphorylated by ***mTOR*** are nPKC.delta., nPKC.epsilon., STAT3, and ***p53*** . The requirement of raptor for binding to and phosphorylation by ***mTOR*** of these potential substrates would clarify their physiol. importance in the ***mTOR*** signaling pathway.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:831120 CAPLUS <<LOGINID::20081217>>
DN 139:394128
TI Loss of Tsc1/Tsc2 activates ***mTOR*** and disrupts PI3K-Akt signaling through downregulation of PDGFR
AU Zhang, Hongbing; Cicchetti, Gregor; Onda, Hiroaki; Koon, Henry B.; Asrican, Kirsten; Bajraszewski, Natalia; Vazquez, Francisca; Carpenter, Christopher L.; Kwiatkowski, David J.
CS Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
SO Journal of Clinical Investigation (2003), 112(8), 1223-1233 CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB Tuberous sclerosis (TSC) is a familial tumor syndrome due to mutations in TSC1 or TSC2, in which progression to malignancy is rare. Primary Tsc2-/- murine embryo fibroblast cultures display early senescence with overexpression of p21CIP1/WAF1 that is rescued by loss of ***TP53*** . Tsc2-/- ***TP53*** -/- cells, as well as tumors from Tsc2+/- mice, display an ***mTOR*** -activation signature with constitutive activation of S6K, which is reverted by treatment with rapamycin. Rapamycin also reverts a growth advantage of Tsc2-/- ***TP53*** -/- cells. Tsc1/Tsc2 does not bind directly to ***mTOR*** , however, nor does it directly influence ***mTOR*** kinase activity or cellular phosphatase activity. There is a marked redn. in Akt activation in Tsc2-/- ***TP53*** -/- and Tsc1-/- cells in response to serum and PDGF, along with a redn. in cell ruffling. PDGFR.alpha. and PDGFR.beta. expression is markedly reduced in both the cell lines and Tsc mouse renal cystadenomas, and ectopic expression of PDGFR.beta. in Tsc2-null cells restores Akt phosphorylation in response to serum, PDGF, EGF, and insulin. This activation of ***mTOR*** along with downregulation of PDGFR PI3K-Akt signaling in cells lacking Tsc1 or Tsc2 may explain why these genes are rarely involved in human cancer. This is in contrast to PTEN, which is a neg. upstream regulator of this pathway.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:809092 CAPLUS <<LOGINID::20081217>>
DN 140:89948
TI The PCPH Oncoprotein Antagonizes the Proapoptotic Role of the ***Mammalian*** ***Target*** of ***Rapamycin*** in the Response of Normal Fibroblasts to Ionizing Radiation
AU Tirado, Oscar M.; Mateo-Lozano, Silvia; Sanders, Sean; Dettin, Luis E.; Notario, Vicente
CS Department of Radiation Medicine, Laboratory of Experimental Carcinogenesis, Georgetown University Medical Center, Washington, DC, 20057-1482, USA
SO Cancer Research (2003), 63(19), 6290-6298 CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Exposure of normal mouse fibroblasts (MEF3T3) to ionizing radiation (IR) resulted in a dose-dependent increase of ***mTOR*** mRNA and protein levels and the shuttling of the ***mTOR*** protein from its normal, predominantly mitochondrial location to the cell nucleus. The same IR doses that activated ***mTOR*** induced the phosphorylation of ***p53*** on Ser18 (mouse equiv. to human Ser15) and the subsequent transcriptional activation of PUMA, a known proapoptotic ***p53*** -target gene, and promoted apoptosis involving increased overall caspase activity, caspase-3 activation, cleavage of poly(ADP-ribose) polymerase (PARP) and classic protein kinase C (PKC) isoforms, and DNA fragmentation. The proapoptotic role of ***mTOR*** in this process was demonstrated by the fact that rapamycin, a ***mTOR*** inhibitor, blocked ***p53*** Ser18 phosphorylation, the induction of PUMA, and all other apoptosis events. Furthermore, the proapoptotic function of ***mTOR*** was also antagonized by the expression in MEF3T3 cells of the PCPH oncoprotein, known to enhance cell survival by causing partial ATP depletion. Tetracyclin (Tet)-regulated expression of oncogenic PCPH, or overexpression of normal PCPH, blocked both phosphorylation and nuclear shuttling of ***mTOR*** in response to IR. These results indicate that alterations in PCPH expression may render tumor cells resistant to IR, and perhaps other DNA-damaging agents, by preventing ***mTOR*** activation and signaling.
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:561516 CAPLUS <<LOGINID::20081217>>
DN 139:274403
TI Regulation and role of ***p21*** and p27 cyclin-dependent kinase inhibitors during hepatocyte differentiation and growth
AU Ilyin, Gennady P.; Glaise, Denise; Gilot, David; Baffet, Georges; Guguen-Guillouzo, Christiane
CS Institut National de la Sante et de la Recherche Medicale , Hopital Pontchaillou, Rennes, 35033, Fr.
SO American Journal of Physiology (2003), 285(1, Pt. 1), G115-G127 CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Unlike a large no. of cell types that undergo terminal differentiation assocd. with permanent withdrawal from the cell cycle, mature quiescent hepatocytes retain high proliferative potential. We report here a specific behavior of members of the Cip/Kip family of cyclin-dependent kinase (Cdk) inhibitors during development of the rat liver and proliferation of normal hepatocytes. Expression of ***p21*** , p27, and p57 transcripts and proteins was downregulated during the differentiation process to low or undetectable levels in adult liver. In contrast to p27, ***p21*** protein increased in a mitogen-dependent manner in isolated hepatocytes and its expression pattern correlated with that of cyclin D1. In proliferating hepatocytes, ***p21*** was predominantly assocd. with cyclin D1, these proteins were colocalized in the nucleus and ***p21*** -assocd. retinoblastoma protein (pRb) kinase activity increased in parallel with that of cyclin D1. Overexpression of ***p21*** in mitogen-stimulated hepatocytes reduced DNA synthesis. In contrast, inhibition of ***p21*** expression by antisense or small interfering RNAs oligonucleotides accelerated S phase entry. Finally, expression of ***p21*** and cyclin D1, but not p27 proteins was regulated by MAPK kinase/extracellular signal-regulated kinase and phosphatidylinositol 3-kinase-ferric-reducing ability power/ ***mammalian*** ***target*** of ***rapamycin*** signal transduction pathways. In conclusion, these results demonstrate a specific and differential regulation of ***p21*** and p27 during hepatocyte differentiation and proliferation that may contribute to the control of quiescent differentiated hepatic cell proliferating activity.
RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:530789 CAPLUS <<LOGINID::20081217>>
DN 139:190858
TI Sustained activation of the JNK cascade and rapamycin-induced apoptosis are suppressed by ***p53*** /p21Cip1
AU Huang, Shile; Shu, Lili; Dilling, Michael B.; Easton, John; Harwood, Franklin C.; Ichijo, Hidenori; Houghton, Peter J.
CS Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SO Molecular Cell (2003), 11(6), 1491-1501 CODEN: MOCEFL; ISSN: 1097-2765
PB Cell Press
DT Journal
LA English
AB Under serum-free conditions, rapamycin, an inhibitor of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***), induces apoptosis of cells lacking functional ***p53*** . Cells expressing wild-type ***p53*** or p21Cip1 arrest in G1 and remain viable. In cells lacking functional ***p53*** , rapamycin or amino acid deprivation induces rapid and sustained activation of apoptosis signal-regulating kinase 1 (ASK1), c-Jun N-terminal kinase, and elevation of phosphorylated c-Jun that results in apoptosis. This stress response depends on expression of eukaryotic initiation factor 4E binding protein 1 and is suppressed by p21Cip1 independent of cell cycle arrest. Rapamycin induces p21Cip1 binding to ASK1, suppressing kinase activity and attenuating cellular stress. These results suggest that inhibition of ***mTOR*** triggers a potentially lethal response that is prevented only in cells expressing p21Cip1.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:262079 CAPLUS <<LOGINID::20081217>>
DN 138:281151
TI Use of ***mTOR*** in apoptosis modulation
IN Hayes, Ian; Kroemer, Guido; Ferri, Karine; Castedo, Maria
PA Eirx Therapeutics Limited, Ire.; L'Institut Gustave Roussy; Le Centre National de la Recherche Scientifique
SO PCT Int. Appl., 75 pp. CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1 PATENT NO. KIND DATE APPLICATION NO. DATE ---------- ---- -------- ---------- -------
PI WO 2003027671 A2 20030403 WO 2002-GB4343 20020925 WO 2003027671 A3 20040311 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG AU 2002329420 A1 20030407 AU 2002-329420 20020925
PRAI GB 2001-23025 A 20010925 WO 2002-GB4343 W 20020925
AB The invention relates to the modulation of apoptosis, in particular to the use of ***mTOR*** in the modulation of syncytial apoptosis. A method for the identification of further mols. involved in apoptosis, and the use ***mTOR*** in the treatment of disease, are also disclosed. In addn., assays assocd. with the identification of such mols. are disclosed.

L7 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:78659 CAPLUS <<LOGINID::20081217>>
DN 138:152194
TI CTCF functions as a critical regulator of cell-cycle arrest and death after ligation of the B cell receptor on immature B cells
AU Qi, Chen-Feng; Martensson, Annica; Mattioli, Michela; Dalla-Favera, Riccardo; Lobanenkov, Victor V.; Morse, Herbert C., III
CS Laboratory of Immunopathology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(2), 633-638 CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The WEHI 231 B cell lymphoma is used as a model of self-tolerance by clonal deletion because B cell receptor (BCR) ligation results in apoptosis. Two crit. events precede cell death: an early rise and fall in expression of MYC and cell-cycle arrest assocd. with enhanced expression of ***p21*** , p27, and ***p53*** . CTCF is a transcription factor identified as a repressor of MYC recently shown to cause cell growth inhibition. The present studies demonstrate that BCR ligation of WEHI 231 as well as of normal immature B cells greatly increased expression of CTCF in assocn. with down-regulation of MYC followed by growth arrest and cell death. Conditional expression of CTCF in WEHI 231 mimicked BCR ligation with activated cells showing repressed expression of MYC, enhanced expression of p27, ***p21*** , ***p53*** , and p19ARF, and inhibition of cell growth and induction of apoptosis. In keeping with a central role for CTCF in control of B cell death, conditional expression of a CTCF antisense construct in WEHI 231 resulted in inhibition of p27, ***p21*** , ***p53*** , and p19ARF in assocn. with enhanced expression of MYC. Activation of the endogenous CTCF locus by BCR ligation was also mimicked by three other routes to apoptotic death in WEHI 231: inhibition of the phosphoinositide 3-kinase or ***mTOR*** /FRAP signaling cascades and treatment with transforming growth factor (TGF)-.beta.. Rapid activation of CTCF by BCR ligation or treatment with TGF-.beta. was suppressed by ligation of CD40. These results demonstrate that CTCF is a common determinant to different pathways of death signaling in immature B cells.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:72679 CAPLUS <<LOGINID::20081217>>
DN 138:332163
TI Insulin-like Growth Factor I-mediated Protection from Rapamycin-induced Apoptosis Is Independent of Ras-Erk1-Erk2 and Phosphatidylinositol 3'-Kinase-Akt Signaling Pathways
AU Thimmaiah, Kuntebommanahalli N.; Easton, John; Huang, Shile; Veverka, Karen A.; Germain, Glen S.; Harwood, Franklin C.; Houghton, Peter J.
CS Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105-2794, USA
SO Cancer Research (2003), 63(2), 364-374 CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The ***mTOR*** inhibitor rapamycin induces G1 cell cycle accumulation and ***p53*** -independent apoptosis of the human rhabdomyosarcoma cell line Rh1. IGF-I and insulin, but not EGF or PDGF, completely prevented apoptosis of this cell line. Because the Ras-Erk1-Erk2 and phosphatidylinositol 3'-kinase (PI3K)-Akt pathways are implicated in the survival of various cancer cells, the authors detd. whether protection from rapamycin-induced apoptosis by IGF-I requires one or both of these pathways. Despite the blocking of Ras-Erk signaling by the addn. of PD 98059 (a MEK1 inhibitor) or by the overexpression of dominant-neg. RasN17, IGF-I completely prevented rapamycin-induced death. Inhibition of Ras signaling did not prevent Akt activation by IGF-I. To det. the role of the PI3K-Akt pathway in rescuing cells from apoptosis caused by rapamycin, cells expressing dominant-neg. Akt were tested. This mutant protein inhibited IGF-I-induced phosphorylation of Akt and blocked phosphorylation of glycogen synthase kinase 3. The prevention of rapamycin-induced apoptosis by IGF-I was not inhibited by expression of dominant-neg. Akt either alone or under conditions in which LY 294002 inhibited PI3K signaling. Furthermore, IGF-I prevented rapamycin-induced apoptosis when the Ras-Erk1-Erk2 and PI3K-Akt pathways were blocked simultaneously. Similar expts. in a second rhabdomyosarcoma cell line, Rh30, using pharmacol. inhibitors of PI3K or MEK1, alone or in combination, failed to block IGF-I rescue from rapamycin-induced apoptosis. Therefore, the authors conclude that a novel pathway(s) is responsible for the IGF-I-mediated protection against rapamycin-induced apoptosis in these rhabdomyosarcoma cells.
RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:906496 CAPLUS <<LOGINID::20081217>>
DN 138:1127
TI Human SMG-1, a novel phosphatidylinositol kinase-related protein kinase, associated with components of the mRNA surveillance complex and involved in the regulation of nonsense-mediated mRNA decay
IN Ohno, Shigeo
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 125 pp. CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1 PATENT NO. KIND DATE APPLICATION NO. DATE ---------- ---- -------- ---------- -------
PI WO 2002095025 A1 20021128 WO 2001-JP10234 20011122 W: AU, CA, US CA 2448186 A1 20021128 CA 2001-2448186 20011122 AU 2002215229 A1 20021203 AU 2002-215229 20011122 JP 2003038189 A 20030212 JP 2002-17466 20020125 US 20040137592 A1 20040715 US 2003-720460 20031124
PRAI JP 2001-156088 A 20010524 WO 2001-JP10234 W 20011122
AB A new member of the phosphatidylinositol kinase (PIK)-related kinase family, human SMG-1, useful in screening a therapeutic and/or a preventive agent for pathol. conditions caused by the formation of an early transcription termination codon due to a nonsense mutation, is disclosed. Antibodies and SMG-1 gene knockout animals are claimed. Nonsense-mediated mRNA decay (NMD) is a conserved surveillance mechanism that eliminates imperfect mRNAs that contain premature translation termination codons (PTCs) and code for nonfunctional or potentially harmful polypeptides. The authors have cloned and characterized a new member of the phosphatidylinositol kinase (PIK)-related kinase family. This gene, which the authors term human SMG-1 (hSMG-1), is orthologous to Caenorhabditis elegans SMG-1, a protein that functions in nonsense-mediated mRNA decay (NMD). CDNA sequencing revealed that hSMG-1 encodes a protein contg. a conserved kinase domain, a C-terminal domain unique to the PIK-related kinases and an FKBP12-rapamycin binding-like domain similar to that found in the PIK-related kinase ***mTOR*** . HSMG-1 phosphorylates hUPF1/SMG-2 in vivo and in vitro at specific serine residues in SQ motifs. HSMG-1 can assoc. with hUPF1/SMG-2 and other components of the surveillance complex. Mutation of conserved residues within the kinase domain of hSMG-1 abolishes both autophosphorylation and substrate phosphorylation, demonstrating that hSMG-1 exhibits intrinsic protein kinase activity. In particular, overexpression of a kinase-deficient point mutant of hSMG-1, hSMG-1-DA, results in a marked suppression of the PTC-dependent .beta.-globin mRNA degrdn.; whereas that of wild-type hSMG-1 enhances it. The authors also show that inhibitors of hSMG-1 induce the accumulation of truncated ***p53*** proteins in human cancer cell lines with ***p53*** PTC mutation. Taken together, the authors conclude that hSMG-1 plays a crit. role in NMD through the direct phosphorylation of hUPF1/SMG-2 in the evolutionally conserved mRNA surveillance complex.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:785480 CAPLUS <<LOGINID::20081217>>
DN 137:261756
TI Sequential involvement of Cdk1, ***mTOR*** and ***p53*** in apoptosis induced by the HIV-1 envelope
AU Castedo, Maria; Roumier, Thomas; Blanco, Julia; Ferri, Karine F.; Barretina, Jordi; Tintignac, Lionel A.; Andreau, Karine; Perfettini, Jean-Luc; Amendola, Alessandra; Nardacci, Roberta; Leduc, Philip; Ingber, Donald E.; Druillennec, Sabine; Roques, Bernard; Leibovitch, Serge A.; Vilella-Bach, Montserrat; Chen, Jie; Este, Jose A.; Modjtahedi, Nazanine; Piacentini, Mauro; Kroemer, Guido
CS Centre National de la Recherche Scientifique, UMR 1599, Institut Gustave Roussy, Villejuif, F-94805, Fr.
SO EMBO Journal (2002), 21(15), 4070-4080 CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB Syncytia arising from the fusion of cells expressing the HIV-1-encoded Env gene with cells expressing the CD4/CXCR4 complex undergo apoptosis following the nuclear translocation of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***), ***mTOR*** -mediated phosphorylation of ***p53*** on Ser15 (p53S15), ***p53*** -dependent upregulation of Bax and activation of the mitochondrial death pathway. P53S15 phosphorylation is only detected in syncytia in which nuclear fusion (karyogamy) has occurred. Karyogamy is secondary to a transient upregulation of cyclin B and a mitotic prophase-like dismantling of the nuclear envelope. Inhibition of cyclin-dependent kinase-1 (Cdk1) prevents karyogamy, ***mTOR*** activation, p53S15 phosphorylation and apoptosis. Neutralization of ***p53*** fails to prevent karyogamy, yet suppresses apoptosis. Peripheral blood mononuclear cells from HIV-1-infected patients exhibit an increase in cyclin B and ***mTOR*** expression, correlating with p53S15 phosphorylation and viral load. Cdk1 inhibition prevents the death of syncytia elicited by HIV-1 infection of primary CD4 lymphoblasts. Thus, HIV-1 elicits a pro-apoptotic signal transduction pathway relying on the sequential action of cyclin B-Cdk1, ***mTOR*** and ***p53*** .
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:579239 CAPLUS <<LOGINID::20081217>>
DN 138:146957
TI Mechanisms of resistance to rapamycins
AU Huang, Shile; Houghton, Peter J.
CS Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105-2794, USA
SO Drug Resistance Updates (2001), 4(6), 378-391 CODEN: DRUPFW; ISSN: 1368-7646
PB Harcourt Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Rapamycins represent a novel family of anticancer agents, currently including rapamycin and its derivs., CCI-779 and RAD001. Rapamycins inhibit the function of the ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***), and potently suppress tumor cell growth by arresting cells in the G1 phase or potentially inducing apoptosis of cells, in culture or in xenograft tumor models. However, recent data indicate that genetic mutations or compensatory changes in tumor cells influence the sensitivity of rapamycins. First, mutations of ***mTOR*** or FKBP12 prevent rapamycin from binding to ***mTOR*** , conferring rapamycin resistance. Second, mutations or defects of ***mTOR*** -

regulated proteins, including S6K1, 4E-BP1, PP2A-related phosphatases, and p27Kip1 also render rapamycin insensitivity. In addn., the status of ATM, ***p53*** , PTEN/Akt, and 14-3-3 are also assocd. with rapamycin sensitivity. To better explore the role of rapamycins against tumors, this review will summarize the current knowledge of the mechanism of action of rapamycins, and progress in understanding mechanisms of acquired or intrinsic resistance.
RE.CNT 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:213341 CAPLUS <<LOGINID::20081217>>
DN 137:226029
TI ***Mammalian*** ***target*** of ***rapamycin*** (***mTOR***): pro- and anti-apoptotic
AU Castedo, M.; Ferri, K. F.; Kroemer, G.
CS Centre National de la Recherche Scientifique, Institute Gustave Roussy, Villejuif, F-94805, Fr.
SO Cell Death and Differentiation (2002), 9(2), 99-100 CODEN: CDDIEK; ISSN: 1350-9047
PB Nature Publishing Group
DT Journal; General Review
LA English
AB A review on the role of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***) in apoptosis. In addn. to its role in the control of net protein synthesis and cell size, ***mTOR*** may have a pleiotropic function in the regulation of cell death. This function appears to depend on the cellular context (cell type and activation state) and on multiple downstream targets including well-known apoptosis-regulatory proteins such as ***p53*** , BAD and Bcl-2.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:775101 CAPLUS <<LOGINID::20081217>>
DN 136:100271
TI Human immunodeficiency virus 1 envelope glycoprotein complex-induced apoptosis involves ***mammalian*** ***target*** of ***rapamycin*** /FKBP12-rapamycin-associated protein-mediated ***p53*** phosphorylation
AU Castedo, Maria; Ferri, Karine F.; Blanco, Julia; Roumier, Thomas; Larochette, Nathanael; Barretina, Jordi; Amendola, Alessandra; Nardacci, Roberta; Metivier, Didier; Este, Jose A.; Piacentini, Mauro; Kroemer, Guido
CS Centre National de la Recherche Scientifique, UMR1599, Institut Gustave Roussy, Villejuif, F-94805, Fr.
SO Journal of Experimental Medicine (2001), 194(8), 1097-1110 CODEN: JEMEAV; ISSN: 0022-1007
PB Rockefeller University Press
DT Journal
LA English
AB Syncytia arising from the fusion of cells expressing a lymphotropic human immunodeficiency virus (HIV)-1-encoded envelope glycoprotein complex (Env) gene with cells expressing the CD4/CXCR4 complex undergo apoptosis through a mitochondrion-controlled pathway initiated by the upregulation of Bax. In syncytial apoptosis, phosphorylation of ***p53*** on serine 15 (p53S15) precedes Bax upregulation, the apoptosis-linked conformational change of Bax, the insertion of Bax in mitochondrial membranes, subsequent release of cytochrome c, caspase activation, and apoptosis. P53S15 phosphorylation also occurs in vivo, in HIV-1+ donors, where it can be detected in preapoptotic and apoptotic syncytia in lymph nodes, as well as in peripheral blood mononuclear cells, correlating with viral load. Syncytium-induced p53S15 phosphorylation is mediated by the upregulation/activation of ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***), also called FKBP12-rapamycin-assocd. protein (FRAP), which coimmunoppts. with ***p53*** . Inhibition of ***mTOR*** /FRAP by rapamycin reduces apoptosis in several paradigms of syncytium-dependent death, including in primary CD4+ lymphoblasts infected by HIV-1. Concomitantly, rapamycin inhibits p53S15 phosphorylation, mitochondrial translocation of Bax, loss of the mitochondrial transmembrane potential, mitochondrial release of cytochrome c, and nuclear chromatin condensation. Transfection with dominant neg. ***p53*** has a similar antiapoptotic action as rapamycin, upstream of the Bax upregulation/translocation. In summary, we demonstrate that phosphorylation of p53S15 by ***mTOR*** /FRAP plays a crit. role in syncytial apoptosis driven by HIV-1 Env.
RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:310081 CAPLUS <<LOGINID::20081217>>
DN 135:116757
TI ***p53*** /p21CIP1 cooperate in enforcing rapamycin-induced G1 arrest and determine the cellular response to rapamycin
AU Huang, Shile; Liu, Linda N.; Hosoi, Hajime; Dilling, Michael B.; Shikata, Takuma; Houghton, Peter J.
CS Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105-2794, USA
SO Cancer Research (2001), 61(8), 3373-3381 CODEN: CNREA8; ISSN: 0008-5472
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AB The relationship between G1 checkpoint function and rapamycin-induced apoptosis was examd. using two human rhabdomyosarcoma cell lines, Rh1 and Rh30, that express mutated ***p53*** alleles. Serum-starved tumor cells became apoptotic when exposed to rapamycin, but were completely protected by expression of a rapamycin-resistant mutant ***mTOR*** . Exposure to rapamycin (100 ng/mL) for 24 h significantly increased the proportion of Rh1 and Rh30 cells in G1 phase, although there were no significant changes in expression of cyclins D1, E, or A in drug-treated cells. To det. whether apoptosis was assocd. with continued slow progression through G1 to S phase, cells were exposed to rapamycin for 24 h, then labeled with bromodeoxyuridine (BrdUrd). Histochem. anal. showed that >90% of cells with morphol. signs of apoptosis had incorporated BrdUrd. To det. whether restoration of G1 arrest could protect cells from rapamycin-induced apoptosis, cells were infected with replication-defective adenovirus expressing either ***p53*** or p21CIP1. Infection of Rh30 cells with either Ad-***p53*** or Ad- ***p21*** , but not control virus (Ad-.beta.-gal), induced G1 accumulation, up-regulation of p21CIP1, and complete protection of cells from rapamycin-induced apoptosis. Within 24 h of infection of Rh1 cells with Ad-***p21*** , expression of cyclin A was reduced by >90%. Similar results were obtained after Ad- ***p53*** infection of Rh30 cells. Consistent with these data, incorporation of [3H]thymidine or BrdUrd into DNA was significantly inhibited, as was cyclin-dependent kinase 2 activity. These data indicate that rapamycin-induced apoptosis in tumor cells is a consequence of continued G1 progression during ***mTOR*** inhibition and

that arresting cells in G1 phase, by overexpression of ***p53*** or p21ClP1, protects against apoptosis. The response to rapamycin was next examd. in wild-type or murine embryo fibroblasts nullizygous for ***p53*** or p21ClP1. Under serum-free conditions, rapamycin-treated wild-type MEFs showed no increase in apoptosis compared to controls. In contrast, rapamycin significantly induced apoptosis in cells deficient in ***p53*** (.apprx.2.4-fold) or p21ClP1 (.apprx.5.5-fold). Infection of ***p53*** -/- MEFs with Ad-***p53*** or Ad- ***p21*** completely protected against rapamycin-induced apoptosis. Under serum-contg. conditions, rapamycin inhibited incorporation of BrdUrd significantly more in wild-type murine embryo fibroblasts (MEFs) than in those lacking ***p53*** or p21ClP1. When BrdUrd was added 24 h after rapamycin, almost 90% and 70% of cells lacking ***p53*** or p21ClP1, resp., incorporated nucleoside. In contrast, only 19% of wild-type cells incorporated BrdUrd in the presence of rapamycin. Western blot anal. of cyclin levels showed that rapamycin had little effect on levels of cyclins D1 or E in any MEF strain. However, cyclin A was reduced to very low levels by rapamycin in wild-type cells, but remained high in cells lacking ***p53*** or p21ClP1. Taken together, the data suggest that ***p53*** cooperates in enforcing G1 cell cycle arrest, leading to a cytostatic response to rapamycin. In contrast, in tumor cells, or MEFs, having deficient ***p53*** function the response to this agent may be cell cycle progression and apoptosis.
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AN 1999:120168 CAPLUS<<LOGINID::20081217>>
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TI Rapamycin causes poorly reversible inhibition of ***mTOR*** and induces ***p53*** -independent apoptosis in human rhabdomyosarcoma cells
AU Hosoi, Hajime; Dilling, Michael B.; Shikata, Takuma; Liu, Linda N.; Shu, Lili; Ashmun, Richard A.; Germain, Glen S.; Abraham, Robert T.; Houghton, Peter J.
CS Dep. Mol. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, 38105-2794, USA
SO Cancer Research (1999), 59(4), 886-894 CODEN: CNREA8; ISSN: 0008-5472
PB AACR Subscription Office
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AB The ***mammalian*** ***target*** of ***rapamycin*** (***mTOR***) has been shown to link growth factor signaling and posttranscriptional control of translation of proteins that are frequently involved in cell cycle progression. However, the role of this pathway in cell survival has not been demonstrated. Here, we report that rapamycin, a specific inhibitor of ***mTOR*** kinase, induces G1 cell cycle arrest and apoptosis in two rhabdomyosarcoma cell lines (Rh1 and Rh30) under conditions of autocrine cell growth to examine the kinetics of rapamycin action, we next detd. the rapamycin sensitivity of rhabdomyosarcoma cells exposed briefly (1 h) or continuously (6 days). Results demonstrate that Rh1 and Rh30 cells were equally sensitive to rapamycin-induced growth arrest and apoptosis under either condition. Apoptosis was detected between 24 and 144 h of exposure to rapamycin. Both cell lines have mutant ***p53*** ; hence, rapamycin-induced apoptosis appears to be a ***p53*** -independent process. To det. whether induction of apoptosis by rapamycin was specifically due to inhibition of ***mTOR*** signaling, we engineered Rh1 and Rh30 clones to stably express a mutant form of ***mTOR*** that was resistant to rapamycin (Ser 2035.fwdarw.Ile; designated ***mTOR*** -rr). Rh1 and Rh30 ***mTOR*** -rr clones were highly resistant (>3000-fold) to both growth inhibition and apoptosis induced by rapamycin. These results are the first to indicate that rapamycin-induced apoptosis is mediated by inhibition of ***mTOR*** . Exogenous insulin-like growth factor (IGF)-I protected both Rh1 and Rh30 from apoptosis, without reactivating ribosomal p70 S6 kinase (p70S6K) downstream of ***mTOR*** . However, in rapamycin-treated cultures, the response to IGF-I differed between the cell lines: Rh1 cells proliferated normally, whereas Rh30 cells remained arrested in G1 phase but viable. Rapamycin is known to inhibit synthesis of specific proteins but did not inhibit synthesis or alter the levels of ***mTOR*** . To examine the rate at which the ***mTOR*** pathway recovered, the ability of IGF-I to stimulate p70S6K activity was followed in cells treated for 1 h with rapamycin and then allowed to recover in medium contg. .gtoreq.100-fold excess of FK506 (to prevent rapamycin from rebinding to its cytosolic receptor FKBP-12). Our results indicate that, in Rh1 cells, rapamycin dissocs. relatively slowly from FKBP-12, with a t1/2 of .apprx.17.5 h. in the presence of FK506, whereas there was no recovery of p70S6K activity in the absence of this competitor. This was of interest because rapamycin was relatively unstable under conditions of cell culture having a biol. t1/2 of .apprx.9.9 h. These results help to explain why cells are sensitive following short exposure to rapamycin and may be useful in guiding the use of rapamycin analogs that are entering clin. trials as novel antitumor agents.
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